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Comparison of Substituent Effects in *cis* and *trans* Formamidines by *ab initio* 3-21G Optimization of Molecular Structures of Fluoro Derivatives and their Protonation Products

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Abstract. The influence of the configuration at the C=N double bond and of substitution at each site of an amidino group on the effect of substituents at the other two sites has been studied by *ab initio* 3-21G optimization for eight derivatives of formamidine (all in the *cis* configuration at the C=N double bond) with up to three fluorine substituents in different combinations, and the corresponding formamidinium cations (protonated at the imino nitrogen). The results were compared with those obtained previously for an identical set of compounds but in the *trans* configuration.The differences between the influence of substitution at various sites in *cis* and *trans* isomers of amidines on basicity, tautomerization, and the geometry of the molecules are discussed.

The configuration of the C=N double bond in amidines has considerable effects not only on the pK_a values of individual amidines and on tautomerization equilibria, but also on the ρ values in the Hammett equation for substitution at the three sites of the amidino group. The sensitivity to the effects of substituents at one site of the amidino group (ρ value) depends on substitution at the other two sites, as it was postulated earlier on the basis of experimental results.

For pairs of both *cis* and *trans* isomers applies: The more basic the amidine is, the larger is the difference between the calculated total energies of the tautomers, *i.e.* the tautomeric equilibrium is shifted towards one of the tautomers.

Calculated energies of protonation show that in the case of amidines containing the electron-withdrawing fluorine substituent at the imino nitrogen the *cis* isomer is more basic and, contrary to expectations, in the pairs **2** and **4** as well as **5** and **7** more stable than the *trans* isomer, which may be explained by intramolecular hydrogen bonding from H to a lone electron pair of the non-neighbouring *syn*-fluorine in the *cis* isomer. In contrast, in other amidines the *trans* isomer is more stable.

The basicity of amidines ($R^4N{=}CR^1{-}NR^2R^3$) depends on the substitution at the three sites: at the imino (im) and amino (am) nitrogen atoms and the functional carbon atom (C). It was shown [2-4] that the pK_a values of trisubstituted amidines containing a substituted phenyl ring at one of the three sites obey the Hammett equation (1).

$$pK_a = pK_a^o - \rho\sigma \qquad (1)$$

We have found that the ρ values, for substitution at one site depend to a considerable degree on polar effects of substituents at the other two sites (*e.g.* the effect of substitution at the imino [5, 6] or amino [7] nitrogen depends on the substituent at the functional carbon atom, and the effect of substitution at one nitrogen atom depends on substitution at the other one [8, 9]). The pK_a values of amidines containing two substituted phenyl rings at two sites do not obey the known dual parameter equation (2) where σ_1 and σ_2 are Hammett

type constants of substituents at these two sites, but the equation (3) with the term μ representing the mutual interaction of substituents.

$$pKa = pK_a^o - \rho_1\sigma_1 - \rho_2\sigma_2 \quad (2)$$

$$pK_a = pK_a^o - \rho_1\sigma_1 - \rho_2\sigma_2 - \mu\sigma_1\sigma_2 \quad (3)$$

In the course of systematic studies on structure-basicity relation in amidines it was found that the ρ value for substitution at one site of the amidino group depends on substitution at the other two sites [4, 9-11]. The more general conclusion has been drawn that the alteration of sensitivity to substituent effects at one site of the amidino group caused by a substituent at another site depends on the substituent at the third site.

Recently it was assumed [9] that the general equation (4) for the prediction of the pK_a values of amidines containing various substituents at the three sites of the amidino group, should contain additional cross-terms representing mutual interaction between substituents for all three combinations of pairs of substitution sites. These terms are in the form $\mu_{k,l}\sigma_k\sigma_l$ where σ_k and σ_l are the σ values of substituents at each pair of the sites (k and l) of the amidino group, and the term $\mu_{k,l}$ represents mutual interaction between substituents at these two sites. Because the μ values for interaction between substituents at two different sites are not the same, for the sake of clarity the subscripts indicate the sites of substituents.

$$pK_a = pK_a^o - \rho_1\sigma_1 - \rho_2\sigma_2 - \rho_3\sigma_3 - \mu_{1,2}\sigma_1\sigma_2 - \mu_{1,3}\sigma_1\sigma_3 - \mu_{2,3}\sigma_2\sigma_3 \quad (4)$$

Equation (4) ensures that in the case of a series where only one substituent is invariant (*e.g.* σ_3 is constant) the observed ρ_1 value (equation 3) will be equal to the expression $(\rho_1 + \mu_{1,3}\sigma_3)$ and the ρ_2 value to $(\rho_2 + \mu_{2,3}\sigma_3)$. In the most often encountered cases, where a substituent at only one site is varied and two other substituents are invariant (*e.g.* σ_2 and σ_3 are constant), a linear equation (1) will be obtained. In such cases the observed pK_a^o value will be equal to the expression $(pK_a^o - \rho_2\sigma_2 - \rho_3\sigma_3 - \mu_{2,3}\sigma_2\sigma_3)$ while the observed ρ value equals $(\rho_1 + \mu_{1,2}\sigma_2 + \mu_{1,3}\sigma_3)$.

Looking for a theoretical support for these experimental results we studied in a preceding work [12] the influence of substitution at all three positions of the formamidine N=C–N group by means of *ab initio* optimization of molecular structures using the 3-21G basis set for 7 differently fluoro-substituted formamidines with up to three fluorine atoms. For this purpose we selected the *trans* configuration, because the energy of the *trans* form for the unsubstituted formamidine was calculated [13] with the same basis set to be lower than for the *cis* form by 0.6 kcal mol^{-1}. In experimental X-ray studies of 18 neutral amidines the preference of the *trans* configuration in the crystal was found [14] in ten cases. By NMR methods was found [15] that in solution, even in cases when both isomers were observed, the *trans* isomers appear to be more stable.

We had shown [12] by calculation that the sensitivity to the effects of substituents (ρ value in the Hammett equation) at one site of the amidino group depends indeed on the effects of substituents at the other two sites, and we have estimated these effects.

However, recent experimental results [10] on the influence of substitution on the basicity of amidines indicated, that for certain amidines the *cis* configuration is more stable than the *trans* form and that amidines may exist as an equilibrium mixture of both isomers. It was assumed that the *cis* or *trans* geometry of amidine molecules may have considerable influence on the sensitivity to the effects of substituents.

This prompted us to make additional 3-21G *ab initio* calculations for all corresponding *cis* isomers and their protonation products, and by comparison of the new results with those obtained earlier for *trans* isomers to find an answer to the following questions:

a) Whether and how *cis/trans* isomerism influences the basicities of amidines.

b) How much differ the estimated ρ values for both isomers.

c) How and to what extent may the substituent at one site of the amidino group in *cis* isomers influence the ρ values for substitution at the other two sites.

d) Whether the configuration at the C=N double bond affects tautomerism.

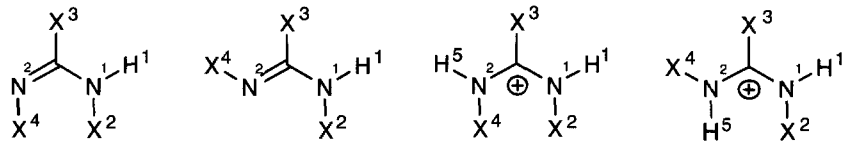
e) How affects the *cis-trans* isomerism at the C=N double bond the molecular geometry.

For the sake of clarity we avoid in this work the use of the E/Z nomenclature because the introduction of fluorine at the carbon atom of formamidine, due to the higher priority of fluorine with respect to nitrogen, changes the notation from Z to E without an actual change of the *cis-trans* geometry at the C=N double bond.

Methods of Calculations

For this study eight *cis* formamidines containing the overall electron-withdrawing fluorine substituent at each of the three amidino sites, and in all possible combinations of substitution at more than one site with the molecular formulae shown in Scheme 1, have been considered as well as the corresponding products of protonation at the imino nitrogen atoms. Sin-

Scheme 1 Molecular formulae, configurations, numbering and abbreviations of the free and protonated *cis*-amidines considered in this work and of the *trans*-amidines treated previously [12]. The numbering of X^4 and H^5 in protonated forms is for formal reasons for the *cis* isomer reverse to that of the *trans* isomer.



cis *trans* *cis* *trans*

free bases **protonated forms**

Compound		Name	X^2	X^3	X^4
1	HHH	Formamidine	H	H	H
2	FHH	N^2-Fluoroformamidine	H	H	F
3	HFH	Fluoroformamidine	H	F	H
4	FFH	(N^2-Fluoro)fluoroformamidine	H	F	F
5	HHF	(N^1-Fluoro)formamidine	F	H	H
6	FHF	N^1,N^2-Difluroroformamidine	F	H	F
7	HFF	(N^1-Fluoro)fluoroformamidine	F	F	H
8	FFF	(N^1,N^2-Difluoro)fluoroformamidine	F	F	F
1p	PHHH	Formamidinium cation	H	H	H
2p	PFHH	N^2-Fluroroformamidinium cation	H	H	F
3p	PHFH	Fluoroformamidinium cation	H	F	H
4p	PFFH	(N^2-Fluoro)fluoroformamidinium cation	H	F	F
5p	PHHF	N^1-Fluoroformamidinium cation	F	H	H
6p	PFHF	N^1,N^2-Difluroroformamidinium cation	F	H	F
7p	PHFF	(N^1-Fluoro)fluoroformamidinium cation	F	F	H
8p	PFFF	(N^1,N^2-Difluoro)fluoroformamidinium cation	F	F	F

gle-determinantal *ab initio* SCF Hartree-Fock MO calculations [16-20] with full optimization of molecular structures have been performed. The analytical gradient optimization procedure of Murtagh and Sargent [21] implemented in Pople's GAUSSIAN 82 program [22] and the split-valence 3-21G basis set [23] have been used in an IBM MVS/XA version on a COMPAREX 7/88 computer [24]. The 3-21G basis set was selected for reasons of economy and to allow comparison with the elaborate calculations of Zielinski and coworkers [15, 25, 26] using this basis set for formamidine and related systems. Calculated molecular geometries and accuracy of related total energies surely depend on the ap-

Table 1 3-21G calculated total energies and protonation energies

Unprotonated *cis* amidines (U)			Protonated *cis* amidines (P)			Protonation energies [a] (U – P) cis	Basicities [b] relative to NH_3 ΔE/kcal mol^{-1}	
Compound		Hartree	Cpd.	Hartree	Hartree	kcal/mol	*cis*	*trans*[c]
1	HHH	-148.23684	**1p**	-148.64351[c]	-0.40667	-255.19	-28.87	-28.29
2	FHH	-246.50642	**2p**	-246.85613	-0.34971	-219.45	6.87	7.06
3	HFH	-246.57319	**3p**	-246.95835[c]	-0.38516	-241.70	-15.37	-10.97
4	FFH	-344.82942	**4p**	-345.16298	-0.33356	-209.32	17.01	18.24
5	HHF	-246.47665	**5p**	-246.85613[c]	-0.37948	-238.13	-11.81	-16.84
6	FHF	-344.72230	**6p**	-345.05482	-0.33252	-208.66	17.66	17.28
7	HFF	-344.80529	**7p**	-345.16298[c]	-0.35769	-224.46	1.86	0.53
8	FFF	-443.03851	**8p**	-443.35443	-0.31592	-198.25	28.08	28.11

[a] 1 Hartree = 627.51 kcal mol^{-1}. [b] Calculated 3-21G protonation energy of NH_3 is –0.36066 Hartree (–226.32 kcal mol^{-1})
[c] Taken from ref. [12].

plied basis set. This influence was studied systematically for CC distances [27] and with 4 basis sets (STO-3G, 3-21G and 6-31G and 6-31G*) for CN compounds [14]. For accurate results on fluorine-substituted compounds, besides large and flexible basis sets, even post Hartree-Fock methods [19, 20] are needed [28]. But for the aim of this work, relating calculated tendencies towards experimental measurements on non identical compounds, the selected 3-21G basis set seems appropriate.

Calculated total energies are given in Table 1, and 3-21G optimized bond distances and bond angles are shown in Tables 3 and 4. Planarity was assumed without calculational proof for the molecules **1** to **4** because this was obtained by optimization in the *trans* series [12]. Compounds **5** to **8** show a change towards tetrahedral geometry at the amino nitrogen atom.

Results and Discussion

Basicities of Amidines

It seems obvious that the basicity of amidines, expressed as pK_a values, are related to corresponding protonation energies, *i.e.* to the differences between 3-21G calculated total energies of the pairs of protonated and unprotonated amidines which are reported in Table 1. For scaling, calculated basicities relative to ammonia are obtained as energies of the reaction shown by equation (5) of proton transfer between ammonia and amidines (amd) in the gas phase at °K.

$$\text{amd} + NH_4^+ \underset{\longleftarrow}{\xrightarrow{K}} \text{amdH}^+ + NH_3 \quad (5)$$

The correspondingly derived values for *cis* isomers are shown in the last but one column of Table 1. When relative basicities of amidines are compared, the lower this value is with respect to NH_3, the more basic is the amidine. If $\Delta E < 0$ the protonated amidine is predicted to be a weaker acid than NH_4^+, or *vice versa* the corresponding amidine is a stronger base than NH_3. These values do not contain any contribution from zero-point vibrations or any entropy or solvent effects, but often in solution changes in entropy parallel those in enthalpy [29]. Basicities of *cis*-formamidines calculated therein can be compared to those of *trans* isomers calculated previously [12] which are presented in the last column of Table 1. The unsubstituted *cis*-formamidine is predicted to be more basic than the *trans* isomer by 0.6 kcal mol^{-1} and substitution by fluorine causes a decrease of basicity in all cases, but this decrease is not the same for both isomers.

All amidine molecules studied lead to the following calculated order of decreasing basicity:
cis-**1** > *trans*-**1** > *trans*-**5** > *cis*-**3** > *cis*-**5** > *trans*-**3** > NH_3 > *trans*-**7** > *cis*-**7** > *cis*-**2** > *trans*-**2** > *cis*-**4** > *trans*-**6** > *cis*-**6** > *trans*-**4** > *cis*-**8** > *trans*-**8**.

cis-Formamidine **1** is calculated to be a stronger base than the *trans* form and this effect is also predicted for **2**, **3**, **4**, and **8** containing the fluorine substituents at the imino nitrogen and/or amidino carbon. The largest difference is observed in **3** for fluorine at the amidino carbon only. Contrary to the amidines **5** to **7**, which contain fluorine at the amino nitrogen atom, the *trans* form is calculated to be more basic with larger differences than in the before mentioned cases.

Relation of Protonation Energies to Hammett ρ Values

The results obtained here provide further support for the conclusion that the alteration of sensitivity by substituent effects (ρ value in the Hammett equation) at one site of the amidino group caused by a substituent at another site depends on the substituent at the third site. They also indicate that – as assumed in an experimental work [10] – the μ values (equations 3 and 4) may be not identical for *cis* and *trans* isomers.

The inter-relation of substituted *cis* amidines **1** to **8** applied to the discussion of mutual interaction of fluorine substituents as shown in Figure 1 is analogous to that for *trans* isomers [12]. Our calculated differences in proton transfer energies reflect changes in ρ values for a hypothetical two point Hammett treatment. For the sake of consistency with experimental work [4] for

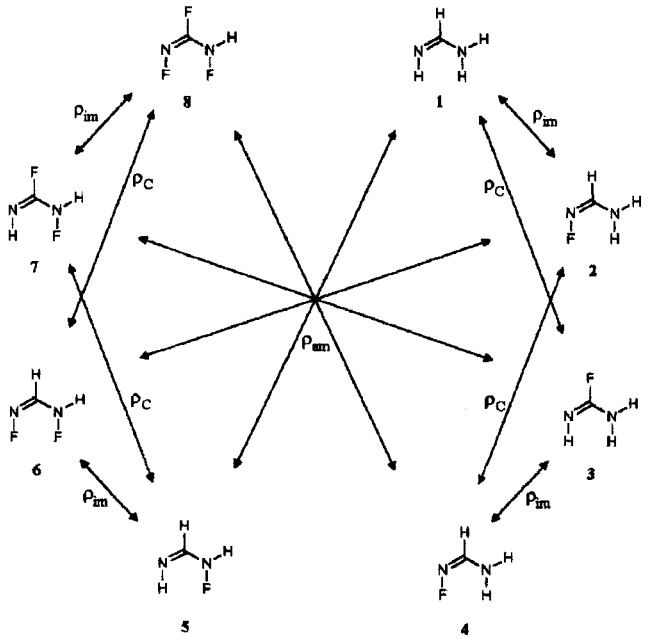


Fig. 1. Selection of pairs of molecules for the estimation of the influence of fluorine substitution at various sites of *cis* isomers on the ρ values .

substitution at imino and amino nitrogens and amidino carbon atom the ρ values are denoted as ρ_{im}, ρ_{am} and ρ_C, respectively. Their numerical values are shown in Table 2.

It is generally assumed on the basis of experimental data that the larger the bond distance between the substituent and the reaction centre is the lower is the ρ value. Calculated results indicate that in the case of both, *cis* and *trans* amidines, indeed the highest ρ values are observed for substitution at the imino nitrogen atom. However, for substitution at the two other sites the order of decreasing ρ values for the two isomers is opposite. Changes in the ρ values caused by influence of substitution by the overall electron-withdrawing substituent fluorine at the second site of the amidino group are represented by the δ values in Table 2. They show that the ρ value observed for one site as a result of substitution at the second site is changed by the same value, which in the empirical relation [equation (3)] is represented by the term $\mu\sigma_1\sigma_2$, and which depends only on the polar effect of the second substituent and its position with respect to the first one.From the graphical presentation (Fig. 2) it is readily seen that the highest μ value is for the pair of substituents at the imino nitrogen and the amidino carbon atom (Fig 2, *a* and *b*). For the pair at the imino and amino nitrogens (Fig. 2, *a* and *c*) it is about two times lower. For the pair at the amidino carbon atom and the amino nitrogen (Fig. 2, *b* and *c*) the value of the term μ is considerably smaller.

This influence is calculated to be different in magnitude for *cis* and *trans* isomers (Δδ values Table 2). Substitution by fluorine at amino nitrogen or amidino carbon causes a decrease of the simulated ρ_{im} value, but for *cis* isomers a stronger effect is observed if the second fluorine is at the amino nitrogen and for *trans* isomers if it is at the carbon atom. It has to be mentioned that in both cases the observed effect is stronger if the second fluorine is in *trans* position with respect to the free electron pair on the imino nitrogen atom.

The ρ_{am} value as a result of substitution by fluorine at the imino nitrogen is decreased for both isomers (for *cis* isomers, where the σ-electron lone pair at imino nitrogen is in *trans* position to the amino nitrogen, this effect is much greater), but surprisingly it is increased by substitution at the carbon atom. The ρ_C value is decreased by substitution at the imino nitrogen (a greater effect is observed for the *trans* isomers) but increased by substitution at the amino nitrogen.

Tautomerization

In both calculated series of *cis* and *trans* amidines two pairs of compounds are tautomeric forms. Compounds **2** and **5** are tautomers of N-fluoroformamidine, whereas **4** and **7** are tautomers of N-fluoro-fluoroformamidine.

$$\underset{\mathbf{2}}{FN{=}CH{-}NH_2} \rightleftharpoons \underset{\mathbf{5}}{FNH{-}CH{=}NH} \qquad (6)$$

$$\underset{\mathbf{4}}{FN{=}CF{-}NH_2} \rightleftharpoons \underset{\mathbf{7}}{FNH{-}CF{=}NH} \qquad (7)$$

Table 2 Influence of substitution by fluorine at various sites of the amidine to simulate ρ values of the Hammett equation (4).

Simulation of	Influence of 2th substituent at	Based on compounds	Simulated ρ values [a]		Simulated μ values (δ) [b]		Δδ [d]
			cis	*trans* [c]	*cis*	*trans* [c]	
ρ_{im}	none	**1** *vs.* **2**	35.74	35.35	0.00	0.00	0.00
	N_{am}	**5** *vs.* **6**	29.47	34.12	–6.27	–1.23	–5.04
	C	**3** *vs.* **4**	32.38	29.21	–3.36	–6.14	2.78
	N_{am}+C	**7** *vs.* **4**	15.14	27.59	–20.60	–7.77	–12.83
ρ_C	none	**1** *vs.* **3**	13.49	17.32	0.00	0.00	0.00
	N_{am}	**5** *vs.* **7**	13.67	17.37	0.19	0.05	0.14
	N_{im}	**2** *vs.* **4**	10.13	11.18	–3.36	–6.14	2.78
	N_{im}+N_{am}	**6** *vs.* **8**	10.41	10.84	–3.08	–6.49	3.41
ρ_{am}	none	**1** *vs.* **5**	17.06	11.44	0.00	0.00	0.00
	C	**3** *vs.* **7**	17.24	11.50	0.18	0.05	0.13
	N_{im}	**2** *vs.* **6**	10.79	10.22	–6.27	–1.23	-5.04
	N_{im}+C	**4** *vs.* **8**	11.07	9.87	–6.99	–1.58	-5.41

[a]) Differences in protonation energies in kcal mol^{-1}. [b]) Differences (δ) between simulated ρ values. [c]) Taken from ref. [12].
[d]) Differences in simulated μ values for *cis* and *trans* isomers, Δδ = δ(*cis*) - δ(*trans*).

It was shown experimentally that the tautomeric equilibrium is related to the basicities of the tautomeric forms and that in the equilibrium mixture of tautomers the less basic tautomer predominates [4, 30]. On the other hand it can be assumed that equilibrium constants are related to the differences in total energies between both tautomers. Calculated differences in total energies are -18.7 kcal mol^{-1} for *cis* and -20.2 kcal mol^{-1} for *trans* isomers in equation (6) and -15.1 kcal mol^{-1} for *cis* and -12.7 kcal mol^{-1} for *trans* isomers in equation (7) indicating that for both isomers the tautomeric equilibrium will be shifted towards the tautomers **2** and **4** which contain the electron-withdrawing substituent at the imino nitrogen atom. However this difference is smaller in the case of the *cis* isomer of equation (6) and reversed

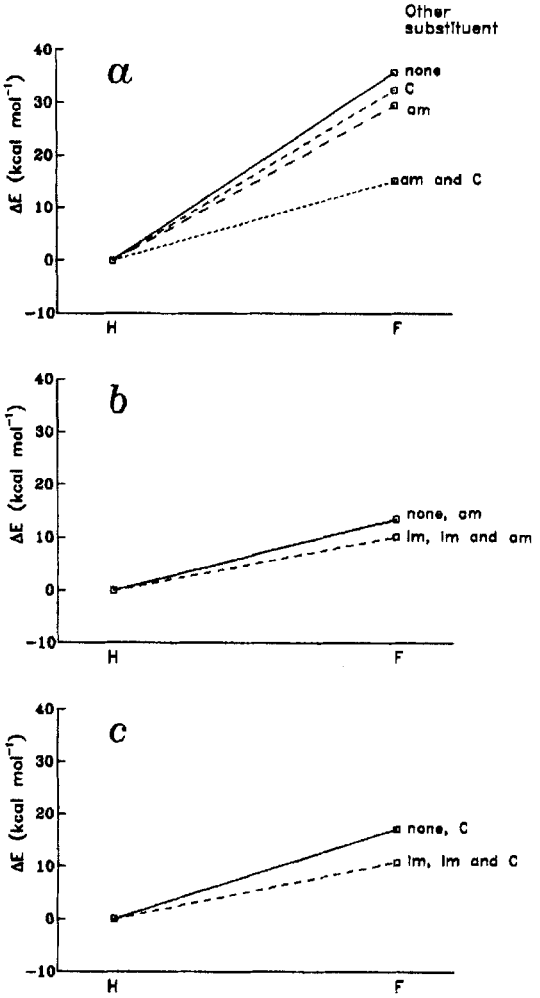


Fig. 2 Simulated ρ values [differences in protonation energies (ΔE kcal mol^{-1}) between amidine with fluorine atom and that with hydrogen at the same site] for fluoro-substituted *cis*-formamidines taken from Table 2

a substitution at the imino nitrogen atom (ρ_{im}),
b substitution at the amidino carbon atom (ρ_C),
c substitution at the amino nitrogen atom (ρ_{am}).

in order for equation (7). This provides further support to our earlier conclusion [12] that the more basic is the amidine the larger is the difference between the energy of the two tautomeric forms and in consequence the higher should be the difference between concentrations of tautomers in the equilibrium mixture.

Configuration at the C=N Double Bond

Contrary to expectations based on steric effects for compounds **2**, **4**, **5**, and **7** the *cis* isomer was calculated to be more stable than the *trans* isomer by 1.3 to 5.0 kcal mol^{-1} (see energies in Table 1 and ref. [12]). Only compounds **1**, **3**, **6**, and **8** show higher stability for *trans* isomers in the range of 0.6 to 4.4 kcal mol^{-1}. The higher stability of *cis* N^2-fluoroformamidines **2** and **4** may be related to the known preferred stability of *cis*-1,2-dihalogen substituted olefins [28, 31, 32] which is difficult to interpret in usual chemical intuitive terms but which can be reproduced by extensive *ab initio* calculations [28]. A recent 3-21G calculation of three push-pull substituted amino ethenes showed also preference of the *cis* (Z) configuration [33].

A convincing explanation, suggested by a referee, is that the C=N *cis* forms **2**, **4**, **5**, and **7** may be stabilized by intramolecular hydrogen bonds from H to a lone electron pair on fluorine, both possible only in non-neighbouring *syn*-orientations of fluorine and hydrogen as may be seen easily on formulae of Fig. 1. This amounts to 3.5 kcal mol^{-1} energetical stabilization for **2**, 3.8 kcal mol^{-1} for **4**, 5.0 kcal mol^{-1} for **5**, and 1.3 kcal mol^{-1} for **7**. In other molecules **1**, **3**, **6**, and **8**, where this effect is lacking, the *trans*-forms at the C=N bond treated in [12] are, as to be expected, more stable by 0.6 to 4.4 kcal mol^{-1}. The same effect is observed with protonation products: The protonated *cis*-forms **2p** and **4p** are stabilized by the same intramolecular hydrogen bonding by 3.7 and 5.0 kcal mol^{-1}. Correspondingly the protonated *trans*-forms **6p** and **8p** of ref. [12] showing the same kind of H-bridge are stabilized by 2.9 and 1.6 kcal mol^{-1}. The protonation of tautomeric formamidines **2** and **5** leads to identical protonation products **2p** and **5p**. Analogously identical pairs **4p** and **7p** are obtained from **4** and **7**. For other *cis-trans* isomers the protonation at imino nitrogen leads to identical products **1p**, **3p**, **5p**, and **7p**.

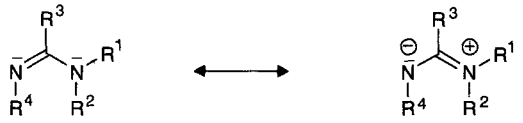
Geometries of the Molecules

The full optimization of molecular geometries leads to additional information by comparison of the calculated influences of fluorine substituents in the *cis* and *trans* series of the amidines on variations of bond lengths,

valence angles, and the question of pyramidality at the amino group.

Bond Distances

In both, *cis* and *trans* amidines, in accordance with classical organic chemistry, the lone electron pair on the amino nitrogen atom is conjugated with the π-electrons of the C=N double bond forming a heteroallylic π-system as shown by equation (8).



(8)

9a **9b**

Substituents at both nitrogen atoms have an influence on the extent of conjugation. Electron-withdrawing substituents at the imino nitrogen atom cause an increase of the conjugation favoring the mesomeric form **9b** and opposite, introduced at the amino nitrogen atom they cause a decrease of conjugation and thus the mesomeric form **9a** is favored. This was shown [12] by calculated variations of bond lengths in the *trans* series of amidines.

As a measure of the degree of conjugation in the amidino group the difference of calculated CN bond distances $\Delta = r_{am} - r_{im}$ as shown in Table 3 may be taken. In the extreme case of the formamidinium cations where bond equalization by conjugation is at maximum, this value is zero. In the other extreme case, with no conjugation between the two CN bonds the amino nitrogen atom should be sp^3 hybridized and the bond distances should correspond approximately to the C–N single bond in methylamine (experimental [34] r = 1.474 Å) and to the isolated C=N double bond in formaldimine (experimental [35] r = 1.273 Å) which lead to an estimate of a maximum experimental value of $\Delta_{max}^{exp} = 0.201$ Å. Optimizations in the 3-21G basis set [36] for these compounds yield 1.472 and 1.256 Å leading to a 3-21G maximum theoretical value of $\Delta_{max}^{3\text{-}21G} = 0.216$ Å.

The Δ values presented in Table 3 show the differences in the degree of conjugation between the *cis* and *trans* series of compounds. In the case of compounds **2**, **4**, **6**, and **8**, where fluorine is present at imino nitrogen, Δ_{trans} is larger than Δ_{cis} *i.e.* the conjugational effect of bond lengths equalization is more pronounced in the *cis* configuration than in the *trans* isomer.

This change of Δ values is due to a reduction of the formal C–N single distances in the *cis* form, if fluorine is introduced at imino nitrogen in compounds **2**, **4**, **6**, and **8**. A small extension of C=N double bonds (0.001 - 0.003 Å) is negligible. The other molecules **1**, **3**, **5**, and **7** show an elongation of C–N single distances while going from *trans* to *cis* isomers, without any change in C=N distances.

Fluorine substitution at the amino nitrogen atom leads to non-planarity and causes, as in the case of *trans* isomers, a decrease of the C=N double bond length by about 0.015 Å (**1** *vs.* **5** and **3** *vs.* **7**) but it leads to an increase of the C–N single bond length of about 0.054 Å (**1** *vs.* **5**) and 0.050 Å (**3** *vs.* **7**), whereas for *trans* isomers [12] this was only 0.04 Å. The bond lengthening is an indi-

Table 3 3-21G calculated bond distances in Å for *cis* amidines (r_{am} and r_{im} = C–N single and C=N double bonds of the amidino group; $\Delta = r_{am} - r_{im}$ = difference of CN bond lengths; X = either H or F).

Compound		$r_{C\text{-}N^1}$	$r_{C=N^2}$	$r_{N^1\text{-}X^1}$	$r_{N^1\text{-}X^2}$	$r_{C\text{-}X^3}$	$r_{N^2\text{-}X^4}$	$r_{N^2\text{-}H^5}$	Δ_{cis}	Δ_{trans} [a]
1	HHH	1.373	1.260	0.995	0.997	1.075	1.015	-	0.113	0.105
2	FHH	1.343	1.274	0.994	0.996	1.070	1.460	-	0.067	0.081
3	HFH	1.360	1.239	0.995	0.994	1.355	1.006	-	0.121	0.111
4	FFH	1.331	1.270	0.995	0.995	1.337	1.452	-	0.061	0.077
5	HHF	1.427	1.245	1.008	1.434	1.073	1.012	-	0.182	0.165
6	FHF	1.384	1.258	1.004	1.418	1.087	1.429	-	0.126	0.134
7	HFF	1.410	1.224	1.007	1.424	1.347	1.006	-	0.186	0.170
8	FFF	1.379	1.250	1.004	1.414	1.341	1.423	-	0.129	0.134
1p	PHHH [a]	1.302	1.302	1.003	1.004	1.071	1.003	1.004	0.000	0.000
2p	PFHH	1.303	1.291	1.003	1.006	1.071	1.397	1.003	0.012	0.004
3p	PHFH [a]	1.295	1.295	1.006	1.003	1.314	1.006	1.003	0.000	0.000
4p	PFFH	1.303	1.284	1.007	1.006	1.308	1.393	1.006	0.019	0.011
5p	PHHF [a]	1.303	1.291	1.003	1.397	1.071	1.003	1.006	0.012	0.011
6p	PFHF	1.293	1.293	1.005	1.392	1.072	1.392	1.005	0.000	0.005
7p	PHFF [a]	1.303	1.284	1.006	1.393	1.309	1.007	1.006	0.019	0.019
8p	PFFF	1.292	1.292	1.008	1.389	1.311	1.389	1.008	0.000	0.007

[a]) Taken from ref. [12].

cation of the change of hybridization at amino nitrogen from sp^2 towards sp^3. As a result the influence on bond lengths due to substitution by a fluorine atom at the amino nitrogen atom is more prominent than that at imino nitrogen. The Δ values of 0.187 and 0.186 Å for compounds **5** and **7** clearly indicate that in this case the conjugation is considerably decreased.

It has to be pointed out that in *cis* as well as in *trans* isomers substitution at the amidino carbon atom has no influence on the difference of the bond lengths, however it definitely has an effect on their absolute values. Substitution by fluorine at the amidino carbon atom in *cis* isomers causes a decrease of both bond lengths by 0.015 Å (**1** *vs.* **3**) and 0.010 Å (**2** *vs.* **4**) for the C–N single bond and even 0.021 Å (**1** *vs.* **3**) and 0.024 Å (**2** *vs.* **4**) for the C=N double bond. These geometrical effects may be generalized: The change of configuration from *trans* to *cis* at the C=N double bond does not affect the length of the C=N bond, but leads to an increase of the C–N single bond of formamidines if hydrogen is the substituent at the imino nitrogen atom and opposite, leads to a decrease of the C–N single bond length, if fluorine is the substituent at the imino nitrogen.

In the protonated forms (amidinium cations (**1p** to **8p**) both CN bond distances are nearly equalized and, as an effect of the fluorine substitution, slightly shortened. The Δ values are all about zero. Closer inspection of Table 3 shows that in the cases of asymmetric substitution with fluorine either in *syn*-periplanar (**5p** and **7p**) or *anti*-periplanar conformations (**2p** and **4p**) the CN bond bearing the fluorine substituent is elongated and the other one is shortened.

Following the X-ray observation of Krygowski and coworkers [37] that in solid-state structures of amidine bases, a shortening of the C–N single bond is related to a lengthening of the C=N double bond, we derived [14] equation (9) for 23 experimental data points of neutral amidines with a linear regression coefficient r = 0.922 and a standard deviation (esd) of 0.009 Å.

$$r_{C=N} = 2.304 - 0.546 \times r_{C-N} \quad (9)$$

For 26 experimental distances of amidinium cations the statistically less precise equation (10) was obtained [14, 37] with R = 0.870 and esd = 0.007 Å.

$$R_{C=N} = 2.304 + 0.807 \times r_{C-N} \quad (10)$$

In this case short bond distances are linearly related to longer distances with a positive slope unequal to unity. Our 3-21G calculated bond lengths for free *cis* amidines yielded similar results as in equation (9) presented by eqn. (11) for 6 data points with a correlation coefficient r = 0.914. The data points for fluorine substituents on the amidino carbon atom (**3** and **7**) like in the case of *trans* amidines owing to operation of the Walsh rules [38, 39] and the change of hybridization from sp^2 to sp^3 are far off the correlation line and have been omitted.

$$r^{cis}_{C=N} = 1.674 - 0.302 \times r^{cis}_{C-N} \quad (11)$$

Table 4 3-21G calculated bond angles for cis amidines (in degrees, X = either H or F).

Compound		H^1N^1C	X^2N^1C	N^1CN^2	X^3CN^1	X^4N^2C	H^5N^2C	$H^1N^1X^2$	$H^5N^2X^4$
1	HHH	120.95	121.39	129.26	112.76	115.50	–	17.66	–
2	FHH	121.82	118.25	127.87	117.71	105.98	–	119.93	–
3	HFH	119.46	121.42	132.26	108.84	117.88	–	119.12	–
4	FFH	120.57	118.32	129.94	114.89	104.11	–	121.11	–
5	HHF	115.30	107.87	127.49	110.74	114.92	–	104.58	–
6	FHF	116.93	113.80	132.96	112.57	111.01	–	106.38	–
7	HFF	116.17	107.01	130.57	106.94	117.43	–	106.86	–
8	FFF	115.74	111.86	133.30	109.96	109.13	–	107.90	–
1p	PHHH [a])	120.86	122.97	125.30	117.29	122.97	120.86	116.17	116.17
2p	PFHH	121.46	121.11	123.52	120.23	115.17	131.14	117.43	113.68
3p	PHFH [a])	119.57	123.17	127.49	116.25	123.17	119.57	117.26	117.26
4p	PFFH	120.34	121.38	125.37	119.38	114.18	129.98	118.28	115.84
5p	PHHF [a])	131.15	115.16	123.51	116.19	121.47	121.09	117.44	113.69
6p	PFHF	128.01	119.06	127.91	116.07	118.97	128.07	112.93	112.96
7p	PHFF [a])	129.96	114.18	125.39	115.23	120.34	121.35	118.31	115.85
8p	PFFF	126.68	118.24	129.24	115.38	118.27	126.66	115.08	115.07

[a]) Taken from ref. [12].

For the series of *trans* formamidines the corresponding linear regression shown in equation (12) with r = 0.945 was obtained [12].

$$r_{C=N}^{trans} = 1.930 - 0.488 \times r_{C-N}^{trans} \quad (12)$$

The application of both equations shows that for identical C=N distances above 1.258 Å (the point of intersection) the C–N distance in the *cis* series is derived to be smaller than in the *trans* series.

For protonated amidines the differences between our 3-21G calculated CN bond lengths (8 data points) did not reveal any correlation (r = 0.279) on account of very small differentiations of bond lengths.

Valence Angles

The most pronounced change of valence angles, shown in Table 4 and ref. [12], associated with the change from a *cis* to a *trans* configuration is calculated for the angle N^1–C–N^2 at the amidino carbon atom. In the *cis* series corresponding angles are 3 to 10 degrees larger than in the *trans* series and related to this change the angle N^2–C–X^3 is decreased.

As already mentioned, the C=N *cis* forms **2**, **4**, **5**, and **7** are stabilized by intramolecular H-bridges from H to a lone electron pair on non-neighbouring *syn*-fluorine. As a consequence this effect leads to smaller N^1–C–N^2 angles in the range of 127.5° to 130.6° for these molecules. In compounds **1**, **3**, **6**, and **8**, without H-bonding, these angles are larger, in the range of 129.3° to 133°. The differences of these angles between the *cis* and *trans* series is 2.8° to 7.0° for the first group with internal hydrogen bonding and 5.5° to 10.2° for the second group without H-bonds. Similarly in corresponding protonated molecules with this kind of H-bonding: **2p**, **4p**, **5p** and **7p**, these angles are smaller between 123.5° and 125.4°, whereas **1p**, **3p**, **6p** and **8p** show larger angles from 125.3° to 129.2°.

Variations of other valence angles are smaller (generally less than 5°) and may differ in sign from *cis* to *trans*. An approximate linear relation is observed between the in-plane angles X^4–N^2–C and X^3–C–N^1, centered at amino N^2 and at amidino C for both the *cis* and *trans* systems.

Conformation at the Amino Nitrogen

Planarity of the molecules **1** to **4** was assumed as a constraint by input geometry because this was calculated for the *trans* series. Fluorosubstituted formamidines **5** to **8** containing a fluorine substituent at the amino nitrogen atom are calculated to be not planar. In Table 5 the sum of three bond angles at the non-planar amino nitrogen atom of compounds **5** to **8** are compared for the *trans* and *cis* configuration which show an increase in the *trans* series for **5** to **7** and a decrease in the *cis* series with the values for the trisubstituted compound **8** being nearly equal and between the values of **6** and **7**. The value of this sum of 328.4° for purely tetrahedral angles is not reached in any of the series. Further evidence of hybridization at the amino nitrogen is provided by the values of the valence bond angles H^1–N^1–C about 116°, as well as the values of angles F^2–N^1–C around 110°, and inner group angle H^1–N^1–F^2 of about 116° as shown in Table 4. Observed values indicate that these angles are also affected by fluorine substitution at the amidino carbon atom.

Table 5 Sum of bond angles (H^1–N^1–C + X^2–N^1–C + H^1–N^1–X^2) at the non-planar amino nitrogen atom (in degrees). Values for a tetrahedral sp^3-atom are 328.2° and for a trigonal sp^2-atom 360°

Compound		*trans*	*cis*
5	HHF	331.1	350.7
6	FHF	332.7	337.1
7	HFF	336.5	330.0
8	FFF	334.1	335.5

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